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Pharmaceutical R&D - Rahway

TO: Tim Rhodes

FROM: Leigh Shultz **DATE:** 30 Jun 2004

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SUBJECT: Physico-chemical characteristics of L-000224715 phosphate salt, monohydrate form

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L-000224715, also known as MK-0431, is a DPP-IV inhibitor for the treatment of Type II Diabetes Mellitus. It was approved for development as a PCC by SARC in January of 2002 and began Phase I clinical trials in July 2002. Phase I and initial Phase II clinical supplies were manufactured with Forms I and III of the anhydrous phosphate salt; a monohydrate was discovered in March 2003, and after analysis of its properties, the decision was made to use the monohydrate for the Phase III and market formulations. This memo describes the chemical and physical properties of the monohydrate form of the monobasic phosphate salt. Polymorph and physical form data contained in this memo supercedes that found in the L-224715 Preformulation Report issued in Sep 2002.

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cc: MK-0431 IDT, S. Karki

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1.0 SUMMARY

This memo summarizes the physico-chemical characterization of the crystalline monobasic monohydrate form of the phosphate salt of L-000224715 (MK-0431). The monohydrate form is a stable, high-melting, non-hygroscopic material with four known anhydrous polymorphs and multiple isomorphic solvates. It is well-soluble in aqueous media across the physiological pH range and has adequate stability in solution below pH 6.

2.0 DESCRIPTION

L-000224715, a DPP-IV inhibitor, is being developed for oral administration as a treatment for Type II (adult-onset) Diabetes Mellitus (T2DM).

2.1 Name, Structure, Formula

L-000224715 has a molecular weight of 407.321 g/mol and a molecular formula of $C_{16}H_{15}F_6N_5O$. The monohydrate form of the monobasic phosphate salt, has a molecular weight of 523.332 g/mol (salt factor 1.285) and the molecular formula $C_{16}H_{20}F_6N_5O_6P$. The structure of L-000224715 is shown in Figure 1, below.

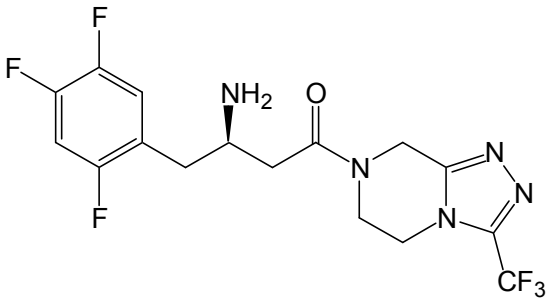

Figure 1. Structure of L-000224715

2.2 Color, Form, Appearance

The monohydrate phosphate salt of L-000224715 is a white, crystalline powder with rod-like individual crystals.

3.0 TEST SUBSTANCES

All experiments were performed on lots of monohydrate phosphate salt (L-000224715-010X) provided by Chemical Engineering R&D. XRPD data were obtained on all lots to confirm form; specific lots for data shown in figures are noted in the text. Thermal characterization (DSC, TGA) was performed on lot 66839-113. Both hygroscopicity and stability data were obtained with lot 66839-123; solubility numbers were obtained with material from lot 66839-142. Some of the data in the polymorph/solvate section was obtained with a lot of the anhydrous material, 006F007. Data obtained from other lots of phosphate salt are noted in the text. Both aqueous solubility as a function of pH and the pKa were determined with the crystalline free base, L-000224715-000T001.

4.0 PHYSICAL CHARACTERIZATION

4.1 Microscopy

Optical microscopy performed on lot L-000224715-66839-142 at 100X magnification (Figure 2) reveals a birefringent, crystalline material. The primary crystals have a well-defined rod-like morphology.

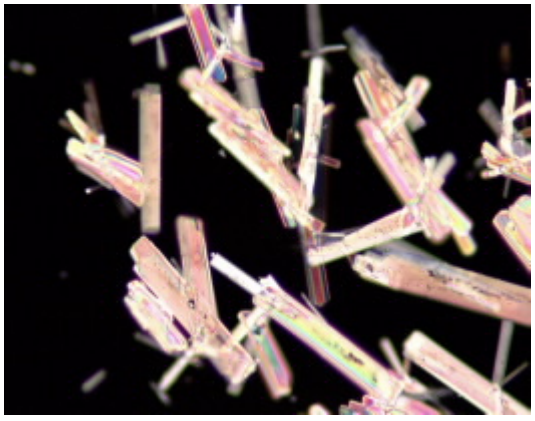

Figure 2. Optical microscopic image of L-000224715 phosphate salt monohydrate (lot 66839-142). Average crystal length is 250 µm.

Two SEM images of a representative lot of L-000224715-010X are shown in Figure 3. The lamellar nature of the individual crystals is evident in this image.

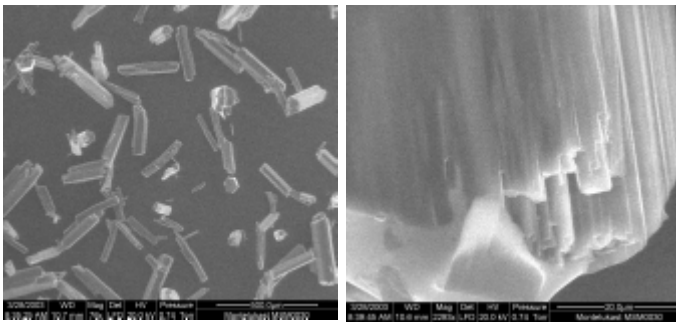

Figure 3. SEM images of L-000224715 phosphate salt monohydrate crystals [76x (left) and 2293x (right) magnification]

Figure 4 shows particle size data for four lots of L-000224715 monohydrate and one lot of anhydrous material, obtained using a MicroTrac light-scattering instrument with isopropanol as the medium. Lot 113 shows a broad, unimodal particle size distribution with a mean of 143 µm after 30 s of sonication (D_{10} = 52 µm, D_{95} = 329 µm). Prior to sonication, the mean particle size was 198 µm, with a D_{10} of 77 µm and a D_{95} of 422 µm. The decrease in both D_{95} and the mean on sonication indicates the friability of the crystals shown in Figure 3. Lots 125 and 144 have similar average particle sizes of 165 and 136 µm, respectively. A representative lot of the anhydrous phosphate salt (lot 006F024, plate-like morphology) had an average particle size of 77 µm after 30 s of sonication.

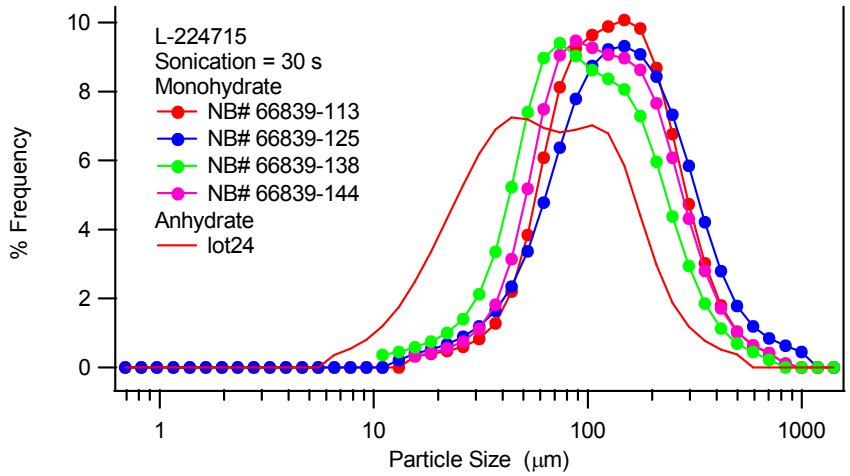

Figure 4. Comparison of particle size distribution for four lots of L-000224715 phosphate salt monohydrate and one lot of anhydrous material

4.2 Differential Scanning Calorimetry (DSC)

A DSC thermogram for lot 66839-142 is shown in Figure 5. Data were obtained by heating a sample in a closed pan at 10 °C/min. The endothermic transition with a maximum at 140.4 °C is due to loss of crystalline water. An endotherm due to melting of Form I is observed at 209.16 °C (onset) with an enthalpy of 243.2 J/g. The endotherm cannot be reliably quantitated due to exothermic decomposition immediately following melting. When the monohydrate is held at 90 °C for 1 hour in the DSC cell (Figure 6), the dehydrated monohydrate is formed. Subsequent heating of the sample at 5 °C/min results in transitions related to formation of a metastable anhydrous form (IV) and then Form I.

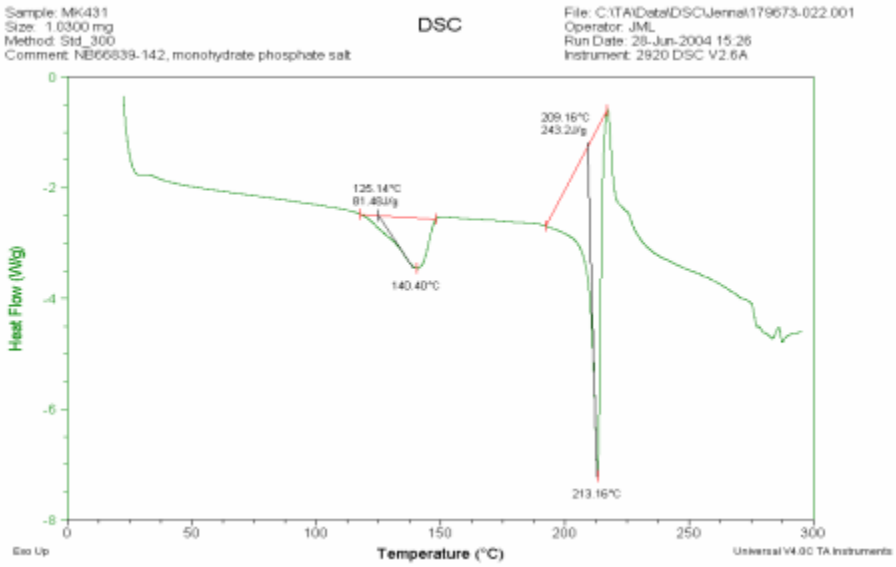

Figure 5. DSC thermogram of L-000224715, lot 66839-142

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